REMARKS

Claims 1-10, 12, 13 and 15-17 were pending. Claim 14 is withdrawn. Applicants hereby cancel claims 19 and 20 without prejudice to Applicants' right to pursue their subject matter in the present application and in related applications. Upon entry of this amendment, claims 1-10, 12, 13 and 15-17 will be pending and presented for consideration.

Telephonic Interview

Applicants thank Examiner Liu and her supervisor for the telephonic interview conducted on September 7, 2006, with Christopher Chung, Brian Fairchild and Fangli Chen. During the interview, it was discussed whether there is a motivation to combine the teachings of cited references U.S. Patent No. 6,190,857 to Ralph ("Ralph") and Liu *et al.*, Infection and Immunity, vol. 69: 2788-2796 (2001) ("Liu") and whether there is a reasonable likelihood of success to carry out Applicants' invention. Applicants offered to submit a declaration from a co-inventor of the present application providing reasonable likelihood of success to carry out Applicants' invention evidence to support that there could be no reasonable likelihood of success to carry out Applicants' invention. Examiner Liu and her supervisor kindly expressed that they will be willing to consider such a declaration together with a response. Applicants have incorporated the interview substance in this response.

Claim Rejections under 35 U.S.C. § 103 over Ralph in view of Liu

Claims 1, 2, 4-7, 9-13 and 16-18 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ralph (U.S. Patent No. 6,190,857) in view of Liu (Infection and Immunity, vol. 69: 2788-2796 (2001)). Claims 11 and 18 were previously cancelled; the rejection with respect to claims 11 and 18 is therefore moot. Applicants respectfully traverse the rejection of the remaining claims for the reasons enumerated below.

The Office action acknowledged that Ralph does not specifically teach using TLR2 in his diagnostic method. Ralph also fails to teach or suggest comparing the expression profiles of any of the other genes listed in Table 4 or Table 6 in peripheral blood samples between patients with a solid tumor or a non-blood disease and disease-free humans as required by independent claims 1 and 16. In attempt to cure the deficiencies of Ralph, the Office action cited Liu to provide disclosure of TLR2 and alleged that because Ralph teaches that the "immune system is an

attractive choice to survey because it would be expected to respond robustly to a malignant disease process," an ordinary skilled artisan would be motivated to compare TLR2 gene expression profile from samples obtained from diseased and healthy individuals (*see*, page 4 of the Office action).

Applicants respectfully disagree with the Office action. Applicants submit that there was no motivation to combine the teachings of Ralph and Liu to arrive at the Applicants' claimed invention. The Manual of Patent Examining Procedure (MPEP) states: "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01(I). Ralph's teaching that "the immune system is an attractive choice to survey" does not amount to a motivation to specifically select TLR2, or any other gene from Table 4 or Table 6, from the thousands of genes expressed in immune system when comparing an expression profile in a peripheral blood sample to a reference expression profile for solid tumor diagnostic purposes. Liu, on the other hand, is directed to understanding the role of TLR2 in the macrophage defense against gram-positive bacteria and large numbers of gram-negative bacteria (*see*, *e.g.*, Liu, abstract and page 2795, left column). Specifically, Liu teaches that TLR2 gene expression is upregulated in macrophage response to peptidoglycan (PGN), a component of the cell walls of gram-positive bacteria, and to high concentrations of lipopolysaccharide (LPS), an integral component of the outer cell membranes of gram-negative bacteria, *in vitro* and *in vivo* and correlates with NF-κB activation (*see*, *e.g.*, Liu, abstract). Liu does not provide any teachings whatsoever with respect to a method for diagnosis of a solid tumor of any sort. Liu therefore does not provide any teaching, suggestion, or motivation, either explicitly or implicitly, that TLR2 should be used as a gene marker for solid tumor diagnosis.

Applicants further submit that there was no reasonable expectation of success that TLR2 could be used as a gene marker for solid tumor diagnosis. The Office action stated that Liu teaches that TLR2 activates NF-κB which is known to be involved in the tumor signaling pathway. "Therefore, a person of ordinary skill in the art would have been motivated to use TLR2 as a genetic marker for cancer because of the involvement of TLR2 in the tumor signaling pathway, and to monitor TLR2 gene expression profile using samples derived from PBMCs to monitor cancer progression and/or diagnosis." *See*, the Office action, page 7. Applicants

respectfully disagree. If the Office action's logic were followed, one would conclude that any genes involved in the NF-κB signaling pathway could be used as a genetic marker for any cancer progression or diagnosis. It is well established that such a conclusion is incorrect. Applicants enclose with this paper a declaration executed by Dr. Michael E. Burczynski, a co-inventor of the present application, under 37 C.F.R. § 1.132. The declaration provides evidence that only a minority of transcripts (6 out of 55) known to be involved in the NF-κB signaling pathway showed statistically significant differential expression in PBMCs of renal cell carcinoma patients as compared to PMBCs of disease-free humans.

Applicants therefore respectfully submit that the Examiner's combination represents a hindsight reconstruction of the invention rather than a proper rejection, based on the perspective of one skilled in the art, as required by § 103. Accordingly, Applicants submit claims 1 and 16 and any claims dependent therefrom are novel and unobvious over Ralph and Liu. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 4-7, 9-13 and 16-18.

Claim Rejections under 35 U.S.C. § 103 over Ralph in view of Golub and Liu

Claims 1-10, 12, 13 and 15-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ralph in view of Golub (Science, Vol. 286:531-527 (1999)) and Liu. Applicants respectfully traverse the rejection for the reasons enumerated below.

As discussed above, claims 1 and 16 and any claims dependent therefrom, including claims 2-10, 12, 13, 15 and 17 are novel and unobvious over Ralph and Liu. Golub does not correct the deficiency of Ralph or Liu.

Golub teaches a method of cancer classification based on gene expression monitoring in tumor samples using DNA microarrays. In particular, Golub compared six normal human kidney biopsies and six kidney tumors (renal cell carcinomas) based on gene expression analysis using DNA microarrays and identified certain genes as class predictors (*see*, Golub, page 531, right column, and note 12). Golub does not teach or suggest comparing an expression profiles of one or more genes listed in Table 4 or Table 6 in peripheral blood samples between patients with a solid tumor and disease-free humans as required by independent claims 1 and 16. Golub also does not teach or suggest that TLR2 or any genes selected from Table 4 or Table 6 can be used as a disease gene for solid tumor diagnosis.

Therefore, Applicants submit claims 1 and 16 and any claims dependent therefrom are novel and unobvious over Ralph, Golub and Liu. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1-10, 12, 13 and 15-17.

CONCLUSION

Applicants believe that all of the art of record has been overcome and claims 1-10, 12, 13 and 15-17 are in condition for allowance. The Examiner is invited to telephone the undersigned agent to discuss any remaining issues. Early and favorable actions are respectfully solicited.

Respectfully submitted,

Date: September 14, 2006
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